UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: **10/11/01**

Subject: HED review of MRID 454761-02 in Response to Bayer's Request to Lower Dermal Absorption Rate from 42% to 21.9%

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HED was asked to conduct an expedited review of the study, "Determination of Exposure During Mixing/Loading and Application of Gusathion WP25 in High Crops " (MRID 454761-02). This review was done in response to Bayer's request that the dermal absorption rate selected by the HIARC for azinphos-methyl (AZM) be reduced from 42% to 21.9%. This review does not include a comprehensive evaluation of the study. For AZM dermal risk assessments, the HIARC had previously selected a dermal absorption rate of 42% based on a rat dermal study using the technical material (100% ai). Bayer proposes that the most appropriate dermal absorption rate for risk assessments is 21.9% based on a study using Guthion 25WP on human volunteers. Based on several limitations of the study, HED concludes that the dermal absorption rate of 21.9% is not supported.

The handler study (MRID 454761-02) submitted to the Agency was conducted in France and Italy. Handler exposure was measured during mixing/loading and airblast application of Gusathion M and Gusathion XL. Both of these products contain 25% of the active ingredient (ai) AZM and are formulated as wettable powders packaged in water soluble bags. In the U.S. there are registrations for the same product, but with 35% and 50% ai (Guthion).

The exposures for eight farmers were monitored for six days while they performed mixing/loading and application with a closed-cab airblast sprayer to apple, peach, and pear trees (5 in France and 3 in Italy). Each of the eight handlers did mixing/loading and application activities. The amount of product handled ranged from 6 to 14 lb ai. The area treated ranged from 8.7 to 23 acres.

The Handlers reportedly wore three layers of clothing consisting of an outer layer (coveralls sectioned into sleeves, torso, and legs), first layer beneath outer layer (jeans and long sleeve shirt) and undergarments (t-shirt, and long pants). Two of the eight study participants did not wear jeans under their coveralls.

Whole-body passive dosimetry (analysis of coveralls, pants, shirt, undergarments) was conducted to estimate dermal exposure. Inhalation exposure sampling was performed using personal air sampling pumps with tenax tubes. During a 6-day period, urine was also collected before, during, and after handler activities and analyzed for the metabolite methylsulfonymethyl-benzamide (Msmb) to estimate the internal dose of AZM.

According to Bayer, a pharmacoknetic study with human volunteers reportedly shows that after one dermal application of AZM, 90% of the total urinary excreted amount is excreted within 4.5 days. The percentage of AZM excretion of the applied dose via the urine and feces is 19.22 and 2.59%, respectively. As the balance for total recovery (including urine, feces, tape stripping, swabs, skin rinsate, gauze, dome and duoderm was 101.9 %, no further correction was used. Thus, 88.1 % of the excreted "azinphos-methyl-equivalents" are excreted via the urine.

Bayer also contends that an analysis of the urine from the pharmacokinetic study with human volunteers has shown that the metabolite methylsulfonymethyl-benzazimide (Msmb) covers 9.2% of the total AZM residue excreted via urine. As this compound was used as a specific marker to AZM, the conversion factor for the total residue in urine is 100/9.2 = 10.87.

HED has not reviewed or validated Bayer's calculations regarding the metabolite Msmb. For the purposes of this review only, HED assumed that the correction factors for excretion via urine as % of total excretion and the percentage of Msmb are 1.14 (100/88.1) and 10.87 (100/9.2), respectively.

A 90 percent field recovery rate was reported for urine biomonitoring samples. Biomonitoring samples were corrected multiplying the residue values by 1.11 (100/90). The LOQ reported for the biomonitoring was 20 Fg/sample. Half of the LOQ (10 Fg) was used for 10 biomonitoring samples reported as less than LOQ (no correction for field recovery was applied to these sample values)

The "internal" dose in "AZM-equivalents" was calculated with the following equation:

AZM Internal dose (Fg)	=	3 AZM equivalents (Fg methylsulfonymethylberizazimide in urine)	x
		correction for field recovery (100/90)	x
		correction for excretion via urine as % of total excretion (100/88.1)	x
		correction for percentage of methylsulfonymethylberizazimide (100/9.2)	

For the undergarment and hand wash samples field recovery rates reported were 78% and 75%, respectively. These samples were corrected for field recovery and values less than the LOQ in the same manner as the biomontoring data. Air monitoring data could not be used to adjust the biomonitoring data so that it reflected dermal only exposure since handlers apparently wore respirators for mixing/loading but not for application.

Bayer suggests that a comparison of the AZM concentration calculated "at skin" from dosimetry/hand

wash data to the internal dose calculated from biomonitoring supports that the human dermal absorption rate of 21.9% is reasonable.

HED's estimate of the AZM "at skin" (from dosimetry and hand wash data) and internal doses (from biomonitoring) were 3.27 and 0.49 Fg/kg bw/day, respectively. A summary of HED's dose calculations are included in Table 1 and 2. The doses calculated indicate a mean dermal absorption of 30.8% (ranging from 8.4 to 58.2) which is higher than the 21.9% suggested by Bayer. HED has concluded that there is insufficient support for using the dermal absorption rate suggested by Bayer (21.9%) based on the "at skin" and internal doses due to the following limitations in the study provided by Bayer:

1. *There is insufficient information regarding the pharmacokinetics of AZM and the metabolite Msmb*. Bayer states that "analysis of the urine from the pharmacokentic study with human volunteers , using the same method as in method MR-052/99, has shown that methyl sulfonymethyl-benzamide accounts for 9.2% of the AZM total residue excreted in the urine." This analysis was not provided in MRID 454761-02, MRID 447858-01 (S. Selim, Absorption, Excretion, Balance and Pharmacokinetics 14C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers, XBL-Study 98052, 1999) or any other document provided to HED. The variability of the metabolite Msmb in the urine of workers as it relates to the total AZM dose is a major concern. Series 875 - Occupational and Residential Test Guideline 875.2600 provides guidance on pharmacokinetics of pesticides and metabolites. Woollen recommends that urinary excretion of the chosen metabolite should account for on average, at least 30% of an orally administered dose, and the range of the chosen metabolite in individuals should not exceed a factor of 3 (Woollen, B.H., 1993, Biological Monitoring for Pesticide Absorption. American Occupational Hygiene 37:525-540).

2. *The number of sample replicates taken does not meet the OPPTS Series 875* - Guidelines. There were only 8 farmers sampled. OPPTS guidelines recommend at least 15 replicates.

3. *There were a large number of non-detects.* Ten of the sixteen undergarment samples (63%) had non-detectable levels, i.e. residues were less than limit of quantification (LOQ). For these samples, half of the LOQ was used for calculating the exposure.

4. *The undergarments samples ("at skin" concentrations) may underestimate exposure.* The undergarment samples represent "at skin" exposure. Study participants wore short-sleeve t-shirt undergarments. The residue on the skin area from the wrist to the end of the sleeve (forearms) was not measured by the t-shirt. The clothing layer above the t-shirt included a long sleeve shirt that did measure the forearm exposure (long-sleeve shirt was touching bare forearm). As the long sleeve shirt was analyzed in one piece and not sectioned, it is not possible to calculate the forearm exposure value. The use of short-sleeve t-shirt undergarment value will likely underestimate the "at skin" exposure which would also translate into an underestimate of the dermal absorption rate.

5. *Undergarments may reduce the amount of AZM that is absorbed by the skin*. The amount of AZM measured in the undergarments theoretically represents the exposure at the skin. However, the undergarment material itself may reduce the amount of AZM available for dermal absorption Different PPE for mixing/loading and application Handlers reportedly wore respirators and

chemical resistant gloves during mixing and loading. The study does not mention what PPE is worn during application but it appears that respirators and chemical resistant gloves were not worn. Inhalation samples were taken throughout mixing/loading and application activities. Therefore, it is not possible to calculate the inhalation doses of the study participants since the application of respirator protection factor would only be applicable to the time spent mixing/loading.

6. *Comparison of biomonitoring (all exposure routes) to dermal dosimetry and hand wash data (dermal only) is not a direct match.* Since the inhalation portion of the dose can not be reliably calculated from the air monitoring data (see above comments on PPE), the biomonitoring data can not be corrected to reflect the dermal only exposure. The registrants suggests that the majority if not 100% of the internal absorbed dose is from the dermal route. The dermal absorption rate calculated may be overestimated if the inhalation portion is not subtracted from the internal dose.

7. *The ratio of dermal passive dosimetry to biomonitoring is an inadequate method for calculating dermal absorption.* A preferred method for quantifying dermal skin absorption would be to apply a known amount of formulation to test subjects with concurrent biomonitoring. There is high amount of uncertainty regarding how much AZM was actually contacting the skin surface.

8. *The dermal absorption is hard to quantify since dermal exposure was so low*. Since handlers wore three layers of clothing and used closed cab tractors the amount of AZM contacting the skin was very low. Therefore a determination of dermal absorption rate from this study has a high degree of uncertainty.

9. *There is a high degree of variability in the dermal absorption calculated*. A mean dermal absorption rate of 30.8% was calculated (ranging from 8.4 to 58.2). The standard deviation was 14.2.

Table 1. Dose and Dermal Absorption Calculations

	Passive Dosimetry and Hand Wash Data											Biomonitoring Data			
	Overalls [1,4]			1st Layer [1,4]		Undergarmets [2,4]		Hand Wash [3,4]	"at skin" AZM conc	Body Weight	"at skin" Dose [5]	Msmb [6]	AZM	AZM Internal Dose [7]	Dermal Absorption [8]
	Sleeves	Torso	Legs	Jeans	Shirt	T-shirt	Pants								
Worker ID	*ug*	*ug*	*ug*	*ug*	*ug*	*ug*	*ug*	*ug*	*ug*	*kg*	*ug/kg bw*	*ug*	*ug*	*ug/kg bw*	*%*
A	5550	3167	6083	158	1165	21.8	21.8	80	124	85	1.45	1.77	29.0	0.34	19.0
B	3350	1967	6183	132	277	23.1	23.1	244	290	74	3.92	7.76	127.0	1.72	30.4
C	1783	787	3250	48	60	< LOQ	< LOQ	75	85	94	0.90	2.62	42.9	0.46	33.6
D	860	197	3017	113	95	< LOQ	< LOQ	63	73	72	1.01	2.31	37.8	0.52	34.2
E	1850	820	2667	70	177	< LOQ	< LOQ	< LOQ	15	85	0.18	1.28	20.9	0.25	58.2
G	7200	2167	27767	-	133	160.3	92.3	1228	1481	92	16.09	8.31	135.9	1.48	8.4
H	2300	2033	5700	-	73	< LOQ	< LOQ	79	89	95	0.93	2.71	44.3	0.47	33.3
I	353	593	1567	77	17	< LOQ	< LOQ	88	98	60	1.63	2.46	40.2	0.67	29.1
										Avg:	3.27			0.74	30.8

[1] Overalls and 1st layer values multiplied by 100/60 (60% field recovery)
[2] Undergarment values multiplied by 100/78 (78% field recovery)
[3] Handwash values multiplied by 100/75 (75% field recovery)
[4] LOQ for dermal dosimetry and hand wash = 10 ug/sample, half LOQ (5 ug/sample) was used for values reported as <LOQ
None of < LOQ values were corrected for field recovery
[5] "at skin" Dose (ug/kg bw) = $\frac{\text{Undergarment (ug) + Handwash (ug)}}{\text{BW (kg)}}$

[6] Biomoinitoring samples multiplied by 100/90 (90% field recovery)

[7] Internal AZM Dose (ug/kg bw) = $\frac{\text{5-day Sum of Msmb (ug) x 100/88.1 x 100/9.2}}{\text{BW (kg)}} \times \frac{\text{AZM Mol Wt (317.3 g*mol}^{-1}\text{)}}{\text{Msmb Mol Wt (239.3 g*mol}^{-1}\text{)}}$

[8] Dermal Absorption % = (Internal AZM Dose/ (Internal AZM dose + "at skin" Dose)) x 100

Workers G and H did not wear jeans.

Table 2. Msmb in Urine Calculations

Worker ID	*Day*	*1st Fg/L*	*2nd Fg/L*	*Mean Fg/L*	*Vol L*	*Fg*	*Correction for 90% Field Recovery Fg*
A	*0*	*<LOQ*	*<LOQ*	*0.10*	*1.15*		
	1	*0.31*	*0.37*	*0.34*	*0.71*	*0.24*	*0.27*
	2	*0.35*	*0.59*	*0.47*	*1.46*	*0.69*	*0.76*
	3	*0.28*	*0.31*	*0.30*	*1.20*	*0.36*	*0.40*
	4	*<LOQ*	*0.20*	*0.15*	*1.10*	*0.17*	*0.18*
	5	*<LOQ*	*<LOQ*	*0.10*	*1.56*	*0.16*	*0.16*
						Total:	*1.77*
B	*0*	*0.84*	*1.03*	*0.94*	*1.53*		
	1	*1.03*	*1.01*	*1.02*	*1.30*	*1.33*	*1.47*
	2	*1.63*	*1.76*	*1.70*	*1.36*	*2.31*	*2.57*
	3	*0.99*	*0.96*	*0.98*	*1.60*	*1.57*	*1.74*
	4	*0.91*	*0.87*	*0.89*	*1.12*	*1.00*	*1.11*
	5	*0.55*	*0.60*	*0.58*	*1.35*	*0.78*	*0.87*
						Total:	*7.76*
C	*0*	*<LOQ*	*<LOQ*	*0.10*	*2.50*		
	1	*0.22*	*0.21*	*0.22*	*2.75*	*0.61*	*0.67*
	2	*0.25*	*0.25*	*0.24*	*2.70*	*0.65*	*0.72*
	3	*0.20*	*0.20*	*0.20*	*3.00*	*0.60*	*0.67*
	4	*<LOQ*	*<LOQ*	*0.10*	*2.93*	*0.29*	*0.29*
	5	*<LOQ*	*<LOQ*	*0.10*	*2.69*	*0.27*	*0.27*
						Total:	*2.62*
D	*0*	*<LOQ*	*<LOQ*	*0.10*	*1.02*		
	1	*0.31*	*0.29*	*0.30*	*1.15*	*0.35*	*0.38*
	2	*0.44*	*0.37*	*0.41*	*1.40*	*0.57*	*0.64*
	3	*0.54*	*0.65*	*0.60*	*1.14*	*0.68*	*0.76*
	4	*0.22*	*0.28*	*0.25*	*0.93*	*0.23*	*0.26*
	5	*<LOQ*	*<LOQ*	*0.10*	*2.69*	*0.27*	*0.27*
						Total:	*2.31*
E	*0*	*<LOQ*	*<LOQ*	*0.10*	*1.76*		
	1	*<LOQ*	*<LOQ*	*0.10*	*1.40*	*0.14*	*0.14*
	2	*0.27*	*0.26*	*0.27*	*1.40*	*0.38*	*0.42*
	3	*<LOQ*	*<LOQ*	*0.10*	*2.06*	*0.21*	*0.21*
	4	*<LOQ*	*<LOQ*	*0.10*	*2.17*	*0.22*	*0.22*
	5	*<LOQ*	*<LOQ*	*0.10*	*2.92*	*0.29*	*0.29*
						Total:	*1.28*
G	*0*	*<LOQ*	*0.20*	*0.15*	*1.65*		
	1	*0.64*	*0.59*	*0.62*	*1.48*	*0.92*	*1.02*
	2	*1.66*	*1.55*	*1.61*	*1.69*	*2.72*	*3.02*
	3	*1.11*	*1.08*	*1.10*	*1.45*	*1.60*	*1.77*
	4	*0.87*	*0.86*	*0.87*	*1.58*	*1.38*	*1.53*
	5	*0.67*	*0.62*	*0.65*	*1.34*	*0.87*	*0.97*
						Total:	*8.31*

Table 2. Msmb in Urine Calculations							
Worker ID	*Day*	*1st µg/L*	*2nd µg/L*	*Mean µg/L*	*Vol L*	*µg*	*Correction for 90% Field Recovery µg*
H	*0*	*<LOQ*	*<LOQ*	*0.10*	*1.20*		
	1	*0.3*	*0.22*	*0.26*	*1.45*	*0.38*	*0.42*
	2	*0.33*	*0.36*	*0.35*	*1.26*	*0.44*	*0.49*
	3	*0.43*	*0.37*	*0.43*	*1.51*	*0.65*	*0.72*
		3rd:	*0.50*				
	4	*0.34*	*0.44*	*0.42*	*1.44*	*0.61*	*0.67*
		3rd:	*0.48*				
	5	*0.37*	*0.32*	*0.35*	*1.05*	*0.37*	*0.41*
						Total:	*2.71*
I	*0*	*<LOQ*	*<LOQ*	*0.10*	*1.01*		
	1	*<LOQ*	*<LOQ*	*0.10*	*1.05*	*0.11*	*0.11*
	2	*0.41*	*0.43*	*0.42*	*0.92*	*0.39*	*0.43*
	3	*0.89*	*0.79*	*0.74*	*1.02*	*0.76*	*0.84*
	4	*0.47*	*0.48*	*0.48*	*1.10*	*0.53*	*0.59*
	5	*0.3*	*0.31*	*0.31*	*1.44*	*0.45*	*0.50*
						Total:	*2.46*